

Hydrocortisone with Fludrocortisone for Adult Patients with Septic Shock: A Systematic Review and Meta-Analysis

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Research

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Abstract

Background : The efficacy of corticosteroids for patients with septic shock remains controversial. Therefore, evaluating a specific corticosteroid treatment could solve the conflicting results of past studies. We performed this systematic review and meta-analysis to elucidate the beneficial effects of a dual corticosteroid treatment regime involving administration of both hydrocortisone and fludrocortisone for adult patients with septic shock on mortality.

Methods : We searched the Medline, Cochrane CENTRAL, and ICHUSHI databases from inception to April 2019. We included peer-reviewed randomized controlled trials that compared the use of both hydrocortisone and fludrocortisone with either corticosteroid-free or hydrocortisone-only treatments on adult patients with septic shock. Three researchers independently reviewed the studies for design, eligibility criteria of patients, dose of each corticosteroid, and duration of corticosteroid therapy following PRISMA guidelines. The random-effects models and Grading of Recommendations Assessment, Development and Evaluation were applied to rate the quality of the evidence. Primary outcome was 28-day mortality, and secondary outcomes were in-hospital mortality, long-term mortality, shock reversal, and adverse events.

Results : Among the four studies eligible for data synthesis, we included 2050 patients from three studies for quantitative synthesis. All studies used similar regimens (50 mg intravenous bolus of hydrocortisone every 6 h and 50 µg tablets of fludrocortisone once daily for 7 days without tapering). The 28-day mortality rate was reduced after dual corticosteroid treatment [risk ratio, 0.88; 95% confidence intervals (CI), 0.78–0.99]. The heterogeneity between the studies was low ($I^2 = 0\%$). Furthermore, the certainty in the effect estimates was high. Patients that underwent dual corticosteroid treatment had lower long-term mortality rates (RR, 0.90, 95% CI, 0.83–0.98) and higher rate of shock reversal after 28 days (odds ratio, 1.06; 95% CI, 1.01–1.12) than control patients. Adverse events (except for hyperglycemia) were similar among the treatment groups.

Conclusions : The available evidence suggests that a combination of fludrocortisone and hydrocortisone is more effective than adjunctive therapy and may be recommended for patients with septic shock.

Background

The beneficial effects of systematic corticosteroid treatment in adult patients with septic shock have been controversial [1–8]. Experimental studies have suggested the presence of pathophysiological changes in the hypothalamic–pituitary–adrenal (HPA) axis in patients with sepsis [9, 10], giving rise to studies focusing on the potential therapeutic role of corticosteroids for sepsis, in particular for patients with septic shock [11–27]. Although corticosteroids have been shown to improve blood pressure [12–14, 16, 21], there are conflicting results on survival benefits in recent large randomized controlled trials (RCTs) and systematic reviews [1–8, 11, 15, 17–20, 22–27], resulting in different clinical guideline recommendations for corticosteroid use in patients with sepsis [28–32].

Some reasons for these contradictory findings include differences in patient populations and the variation in corticosteroid treatments. Low-risk-of-bias (RoB) RCTs recruited only patients with septic shock and investigated mortalities as their primary outcomes; however, their definition of refractory shock differed in the doses of vasopressors required [15, 19, 26, 27, 33]. The durations, amounts, and type of corticosteroids also differed, due to which optimal corticosteroid treatments remain unclear [26, 27, 33, 34]. Moreover, most systematic reviews involved heterogeneous studies, and they examined specific populations or particular corticosteroid therapies only through subgroup analyses [5, 6, 8].

Among the various corticosteroid treatments, the dual treatment with hydrocortisone and fludrocortisone for septic shock has shown promising results; one large RCT in 2018 found that administration of both hydrocortisone and fludrocortisone reduced the 90-day mortality of patients with septic shock [27]. Hydrocortisone, the name for cortisol hormone as a medication, has both glucocorticoid and mineralocorticoid activities; whereas fludrocortisone, a synthetic corticosteroid, possess very potent mineralocorticoid activity [35–38]. While hydrocortisone has been extensively examined in sepsis, fludrocortisone has been used for patients with aldosterone deficiency, and the dual administration of these two medications is recommended for some patients with primary adrenal insufficiency [39, 40]. Considering that patients with septic shock have been found to have unexpectedly low aldosterone levels due to HPA axis abnormalities [41], dual treatment with hydrocortisone and fludrocortisone should be further validated as a type of corticosteroid treatment for septic shock.

Accordingly, we conducted a systematic review and meta-analysis to identify beneficial effects of the dual treatment with hydrocortisone and fludrocortisone for patients with septic shock, when compared to treatment with placebo or hydrocortisone alone. We particularly examined clinically significant outcomes such as mortality, vasopressor withdrawal, and adverse events (AEs).

Methods

We report our findings in this review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Guidelines. The review protocol has been registered with PROSPERO (reference CRD42019139069). Substantive deviations from the published protocol are highlighted with accompanying explanations.

Search Strategy

Three databases were searched in April 2019: Medline, Cochrane CENTRAL, and ICHUSHI. Our search strategy included Medical Subject Headings search terms and keywords. Search terms were selected for two domains: 1) patient populations (e.g., “sepsis,” “systemic inflammatory response syndrome,” “organ failure,” or “critical illness”) and 2) dual corticosteroid treatment as intervention (e.g., “hydrocortisone” AND “fludrocortisone”). Search strategies are shown in Supplemental Tables 1 and 2. We also evaluated the reference list of the relevant studies to identify additional sources [3, 5, 6, 8].

Study Selection

We included RCTs that fulfilled the following criteria: 1) full-text publication in peer-reviewed journals in English; 2) inclusion of adult patients diagnosed with septic shock, according to accepted criteria; and 3) studies comparing the use of both hydrocortisone and fludrocortisone with a corticosteroid-free or hydrocortisone-only comparator group. We excluded studies that did not meet those three criteria.

After implementation of the search strategy, reviewers performed screenings in duplicate in two stages. First, two independent reviewers (IN and MT) assessed titles and abstracts of the retrieved literature to identify potentially relevant articles. Then, the reviewers obtained full texts of articles for those possibly eligible for further review and independently assessed them. We recorded reasons for exclusion at the full article review stage. Disagreements between the two reviewers were resolved through discussion among them and a third reviewer (RY) until consensus was achieved.

Data Extraction and Quality Assessment

The three reviewers extracted the data independently and in duplicate using predefined data abstraction forms. Any discrepancies were resolved by group discussion. The extracted data for each study included the first author, year of publication, study design, number of study sites, number of patients, eligibility criteria for patients, demographic data, type of corticosteroids given to patients, dose of each corticosteroid, and duration of corticosteroid therapy. In addition, researchers also extracted the following clinical outcomes: 28-day mortality as short-term mortality, in-hospital mortality, long-term mortality (longer than 90 days), shock reversal, and any AEs related to the corticosteroid therapy.

RoB was then evaluated, independently and in duplicate, for each outcome of individual studies using the Cochrane risk of bias assessment tool, which assesses randomization, allocation concealment, blinding of the study participants and personnel, blinding of the outcome assessments, incomplete outcome data, selective outcome reporting, and other potential sources of bias [42]. Disagreements for RoB were resolved by discussion.

Data Synthesis and Analysis

The primary outcome was 28-day mortality. The secondary outcomes included in-hospital mortality, long-term mortality (longer than 90 days), shock reversal at day 28 defined as vasopressor withdrawal at day 28, vasopressor-free days up to day 28, and the prevalence of AEs such as superinfection, gastrointestinal (GI) bleeding, hyperglycemia, hyponatremia, and any other events related to corticosteroid treatment. Subgroup analyses were prespecified according to duration of treatment and dose of hydrocortisone and/or fludrocortisone. Sensitivity analyses were performed by repeating meta-analyses, in which we defined control groups as either patients not treated with corticosteroid (placebo) or patients treated only with hydrocortisone (hydrocortisone-only).

We used the Review Manager software (RevMan, Version 5.3: The Cochrane Collaboration, Copenhagen, Denmark) to conduct the meta-analyses. We used a random-effects model to calculate pooled effect sizes and corresponding 95% confidence intervals (CIs) for outcomes in which nonidentical effects of intervention were estimated between studies, whereas we used a fixed-effects model for shock reversal at

day 28, in which the effect of intervention was estimated to be in the same direction based on previous studies [1–8]. We presented results as risk ratios (RRs) for dichotomous outcomes and as mean differences (MDs) for continuous outcomes. Extracted data provided as medians with interquartile ranges were changed into means with standard deviation [43]. Heterogeneity between studies was assessed using χ^2 test for homogeneity, I^2 statistic, and visual inspection of the forest plots. We considered the heterogeneity of I^2 values < 25% as low, those between 25 and 50% as moderate, and those > 50% as high. Publication bias was also evaluated by a funnel plot.

The overall certainty of evidence for each outcome was assessed and rated as high, moderate, low, or very low using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach based on study limitations, inconsistency, indirectness, and publication bias (44). Disagreements for GRADE assessment were resolved by group discussion.

Results

Study Selection

We identified 94 articles through the Medline search, 35 through the Cochrane CENTRAL search, and two articles through the ICHUSHI search. Eleven studies were considered potentially eligible; then, we excluded seven after the full-text screening (two non-full-text articles, three non-RCTs, one non-English study, and one study with a different intervention). Among four studies eligible for data synthesis, we included a total of 2050 patients from three studies for our quantitative synthesis (one study did not report any primary or secondary outcome data; Fig. 1).

Description of Eligible Studies

Supplemental Table 3 presents a detailed description of the eligible studies [15, 27, 45, 46]. All studies were conducted at multiple centers, and their eligibility criteria for patients included the requirement of vasopressors to define septic shock. All studies also used the same intervention protocol in terms of type, dose, and duration of the corticosteroid therapy; hydrocortisone was administered as a 50 mg intravenous bolus every 6 h, and fludrocortisone as a 50 μ g tablet through a nasogastric tube once daily for 7 days (without tapering). Three of the eligible studies used placebo for the control group [15, 27, 46], and the other used the hydrocortisone alone therapy (a 50 mg intravenous bolus every 6 h) for the control group [45]. One of the eligible studies reported only hematological and biochemical outcomes [46] obtained from the same population of another included study [15]; therefore, we did not include it in the quantitative synthesis.

Primary Outcome

Two studies reported 28-day mortalities [15, 27], and our analyses showed the 28-day mortality rate was lower in the dual corticosteroid treatment patients than in the controls, and the RR of 28-day mortality was 0.88 (95% CI = 0.78–0.99) with low heterogeneity (I^2 = 0%, p = 0.79; Fig. 2). Publication bias was not

estimated using the funnel plot because only two studies were included in the meta-analysis. Prespecified subgroup analysis was not performed regarding the primary outcome because the duration and dose of the corticosteroid treatments were identical between the two studies. Furthermore, sensitivity analysis was not performed on primary outcome because the control groups of both studies were cortisol-free (placebo) populations.

Secondary Outcomes

In-hospital mortalities and long-term mortalities were reported in three studies [15, 27, 45]. In-hospital and long-term mortalities were lower in the patients treated with both hydrocortisone and fludrocortisone (RR = 0.89, 95% CI, 0.81–0.97 and RR = 0.90, 95% CI, 0.83–0.98, respectively) with low heterogeneity (Supplemental Fig. 1).

Shock reversal at day 28 was reported in two included studies, whereas vasopressor-free days of up to day 28 were reported in only one included study. Patients in the dual corticosteroid treatment group had a higher rate of shock reversal (RR = 1.06, 95% CI, 1.01–1.12) [15, 27] and more vasopressor-free days (MD = 2.0 days, 95% CI, 0.8–3.2 days) [27] than patients in the control group (Fig. 3).

Meta-analyses on AEs by corticosteroid treatment revealed that risks of superinfection [15, 27, 45], GI bleeding [15, 27], and psychiatric disorder [15] were similar between the dual corticosteroid treatment and the control groups (Supplemental Fig. 2). The incidence of hyperglycemia was higher in patients treated with both hydrocortisone and fludrocortisone, although only one study reported hyperglycemia as an AE [27] (Supplemental Fig. 2).

We did not perform prespecified subgroup analyses on secondary outcomes because the duration and dose of corticosteroid treatments were identical among all included studies. Sensitivity analyses were performed on in-hospital mortality, long-term mortality, and superinfection because the control groups comprised both corticosteroid-free population and hydrocortisone-only population. Meta-analyses comparing the dual corticosteroid treatment with placebo showed that in-hospital and long-term mortalities were lower in the dual corticosteroid group than in the placebo group (RR = 0.88, 95% CI, 0.80–0.98 and RR = 0.89, 95% CI, 0.81–0.97, respectively), whereas AEs were comparable between the groups [15, 27] (Supplemental Fig. 3). A sensitivity analysis comparing the dual corticosteroid treatment with hydrocortisone-only therapy revealed a higher superinfection rate in the dual corticosteroid treatment group (RR = 1.54, 95% CI = 1.05–2.26), whereas in-hospital and long-term mortalities were comparable between the groups [45] (Supplemental Fig. 4). Table 1 summarizes results according to control groups.

Risk of Bias and Summary of Findings

A summary of the RoB analysis results is shown in Supplemental Fig. 5. The RoB for mortality was evaluated as “low” for all components of the Cochrane risk of bias assessment, with the exception of the “unclear risk” at “selective outcome reporting” in the study by Annane et al [15] in 2002.

The quality of evidence for each outcome is summarized in Table 2, in which we evaluated the certainty of effect estimates using the GRADE approach. The 28-day and long-term mortalities were significantly reduced by the dual administration of both hydrocortisone and fludrocortisone with high certainty. Among the AEs associated with corticosteroid treatment, the incidence of hyperglycemia was increased by the dual corticosteroid treatment with high certainty.

Discussion

We conducted the current systematic review and meta-analysis to evaluate the effects of dual corticosteroid treatment in terms of clinical outcomes in patients with septic shock. While previous systematic reviews had shown conflicting results, we found a reduced mortality with high certainty: 28-day, in-hospital, and long-term (later than 90 days) mortalities were reduced by the treatment with both hydrocortisone and fludrocortisone.

The main difference between the current study and other meta-analyses is the fact that we examined only the effects of the dual corticosteroid treatment for septic shock. The idea behind the addition of fludrocortisone to hydrocortisone, used as glucocorticoid replacement therapy in patients with adrenal insufficiency, is to enhance the mineralocorticoid activity [35–37]. The biological activity of mineralocorticoids is mediated by the mineralocorticoid receptor (MR) [35, 47], which exists in various organs, such as the kidneys, cardiovascular, immune, and central nervous systems [48, 49]. Animal studies found an association between sepsis and the downregulation of the MR in endothelial cells [50], and mineralocorticoid supplementation lowered IL-6 levels, hastened shock reversal, and improved survival [51, 52]. Some clinical studies also revealed inappropriately low aldosterone levels in patients with septic shock, suggesting an impaired adrenal synthesis of aldosterone, that might be associated with increased mortality [41, 53]. Although the direct effect of mineralocorticoids in septic patients has not been fully elucidated, our results support a recommendation for the dual administration of hydrocortisone and fludrocortisone to patients with septic shock.

The meta-analyses on the secondary outcomes found that the incidence of AEs was not increased by the dual corticosteroid treatment, except that for hyperglycemia, which is consistent with the results of a systematic review examining all types of corticosteroid therapies for sepsis [5]. In that study, the risks for hyperglycemia, hyponatremia, and neuromuscular weakness were similarly increased by the corticosteroid administration, while the incidence of superinfections, GI bleeding, and psychiatric disorders remained similar to those in control patients. Although there may be additional adverse event risks by adding fludrocortisone on hydrocortisone, our sensitivity analysis comparing the dual corticosteroid treatment with hydrocortisone-only therapy identified only higher superinfection rates in the dual corticosteroid treatment group. Considering that MRs are expressed in monocytes and macrophages that undergo a pro-inflammatory polarization in response to mineralocorticoids [54, 55], pathophysiological immunomodulatory changes by the additional mineralocorticoid administration should be further examined.

The recommendation of fludrocortisone use in a previous version of the Surviving Sepsis Campaign guidelines was an optional addition to low-dose hydrocortisone [56], and it got removed from the most recent guidelines in 2016 [28]. Two recent systematic reviews analyzed the dual administration of hydrocortisone and fludrocortisone in subgroup analyses that evaluated heterogeneity in types of corticosteroid treatments, and did not find a credible effect of the specific type of corticosteroid treatment [5, 8]. However, these analyses did not examine the direct association between the dual corticosteroid treatment and clinical outcomes, and based on our results the dual corticosteroid treatment (adding fludrocortisone to hydrocortisone) should be considered more than just an adjunctive therapy.

The results in this study must be interpreted within the context of the study design. We found only four eligible studies and included only two in the meta-analysis for the primary outcome [15, 27], in part because the additional fludrocortisone has not been extensively examined and because we considered only RCTs. However, our search strategy used a wide variety of search terms and the eligibility criteria were wide enough to capture an article by Laviolle et al [46] that was not included in the recent systematic reviews [5–8]. Also, the primary outcome had no heterogeneity and we evaluated the RoBs of the studies included as “low” using the Cochrane risk of bias assessment tool.

Another limitation of this study is the fact that the control group in the meta-analyses consisted of both corticosteroid-free and hydrocortisone-only populations, which may hamper the interpretation of our results. Although some secondary outcomes such as in-hospital and long-term mortalities and superinfection differed in the sensitivity analyses according to the definitions of the comparator group, the reduced 28-day mortality by the dual corticosteroid therapy resulted only from the comparison with placebo administration. Considering that the current study aimed to find beneficial effects of the dual administration of hydrocortisone and fludrocortisone (rather than effects directly related to only fludrocortisone), we believe that this specific corticosteroid therapy can be recommended for patients with septic shock with high quality of evidence.

Moreover, all eligible studies used the same intervention protocol in terms of type, dose, and duration of the corticosteroid therapy. Although different doses of hydrocortisone and/or fludrocortisone might affect the results, the doses used were those standardly used in the replacement therapy for primary adrenal insufficiency [40, 57]. Given that a study on different hydrocortisone-only treatment durations for septic shock revealed no differences in outcomes between 3-day and 7-day regimens [58], a shorter regimen of the dual corticosteroid treatment may be effective and should be investigated.

Conclusions

This systematic review and meta-analysis clarified that hydrocortisone and fludrocortisone treatment reduce the 28-day mortality of patients with septic shock with minimum risk of AEs. Therefore, we recommend this specific corticosteroid treatment for septic shock with high certainty in effect estimates. The pathophysiological mechanisms of the additional fludrocortisone and the duration of treatment should be further studied.

Abbreviations

AE	Adverse events
CI	Confidence intervals
CIRCI	Critical illness-related corticosteroid insufficiency
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
MD	Mean differences
MR	Mineralocorticoid receptor
RCT	Randomized controlled trials
RoB	Risk-of-bias
RR	Risk ratios
SCCM	Society of Critical Care Medicine

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

Dr. Fujishima has received personal fees from Asahi Kasei Japan and Takeda Pharmaceutical, grants from Chugai Pharmaceuticals, Daiichi-Sankyo, Otsuka Pharmaceutical, Pfizer, Astellas Pharma, Shionogi, and Teijin Pharma outside the submitted work. Dr. Masuda reports grants from JIMRO Co., Ltd, and personal fees from MSD K.K, Japan Blood Products Organization, and Asahi Kasei Pharma outside the submitted work.

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Authors' contributions

RY, TF, YM, and SF had the idea for the article. RY, IN, and MT performed the literature search and data analysis. RY drafted the manuscript and IN, MT, TF, YM, and SF critically revised the work.

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Not applicable

References

1. Annane D, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA*. 2009;301:2362-75.
2. Sligl WI, Milner DA Jr, Sundar S, Mphatswe W, Majumdar SR. Safety and efficacy of corticosteroids for the treatment of septic shock: a systematic review and meta-analysis. *Clin Infect Dis*. 2009;49:93-101.
3. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating sepsis. *Cochrane Database Syst Rev*. 2015;12:CD002243.
4. Volbeda M, Wetterslev J, Gluud C, Zijlstra JG, van der Horst IC, Keus F. Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2015;41:1220-34.
5. Rochweg B, Oczkowski SJ, Siemieniuk RAC, Agoritsas T, Belley-Cote E, D'Aragon F, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. *Crit Care Med*. 2018;46:1411-20.
6. Fang F, Zhang Y, Tang J, Lunsford LD, Li T, Tang R, et al. Association of corticosteroid treatment with outcomes in adult patients with sepsis: A systematic review and meta-analysis. *JAMA Intern Med*. 2019;179:213-23.
7. Ni YN, Liu YM, Wang YW, Liang BM, Liang ZA. Can corticosteroids reduce the mortality of patients with severe sepsis? A systematic review and meta-analysis. *Am J Emerg Med*. 2019;37:1657-64.
8. Rygård SL, Butler E, Granholm A, Møller MH, Cohen J, Finfer S, et al. Low-dose corticosteroids for adult patients with septic shock: A systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2018;44:1003-16.
9. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. *J Clin Endocrinol Metab*. 2006;91:3725-45.

10. Mesotten D, Vanhorebeek I, Van den Berghe G. The altered adrenal axis and treatment with glucocorticoids during critical illness. *Nat Clin Pract Endocrinol Metab.* 2008;4:496-505.
11. Cooperative Study Group. The effectiveness of hydrocortisone in the management of severe infections: a double-blind study. *JAMA.* 1963;183:462-5.
12. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med.* 1998;26:645-50.
13. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med.* 1999;27:723-32.
14. Chawla K, Kupfer Y, Goldman I, Tessler S. Hydrocortisone reverses refractory septic shock. *Crit Care Med.* 1999;27:33A.
15. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA.* 2002;288:862-71.
16. Oppert M, Schindler R, Husung C, Offermann K, Gräf KJ, Boenisch O, et al. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. *Crit Care Med.* 2005;33:2457-64.
17. Tandan S, Guleria R, Gupta N. Low dose steroids and adrenocortical insufficiency in septic shock: a double-blind randomised controlled trial from India. *Am J Respir Crit Care Med.* 2005;171:43A.
18. Cicarelli DD, Vieira JE, Benseñor FE. Early dexamethasone treatment for septic shock patients: A prospective randomized clinical trial. *S Paulo Med J.* 2007;125:237-41.
19. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med.* 2008;358:111-24.
20. Hu B, Li JG, Liang H, Zhou Q, Yu Z, Li L, et al. The effect of low-dose hydrocortisone on requirement of norepinephrine and lactate clearance in patients with refractory septic shock. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue.* 2009;21:529-31.
21. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest.* 2007;131:954-63.
22. Arabi YM, Aljumah A, Dabbagh O, Tamim HM, Rishu AH, Al-Abdulkareem A, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. *CMAJ.* 2010;182:1971-7.
23. Tongyoo S, Permpikul C, Mongkolpun W, Vattanavanit V, Udompanturak S, Kocak M, et al. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. *Crit Care.* 2016;20:329.
24. Keh D, Trips E, Marx G, Wirtz SP, Abduljawwad E, Bercker S, et al. Effect of hydrocortisone on development of shock among patients with severe sepsis: the HYPRESS randomized clinical trial. *JAMA.* 2016;316:1775-85.

25. Lv QQ, Gu XH, Chen QH, Yu JQ, Zheng RQ. Early initiation of lowdose hydrocortisone treatment for septic shock in adults: a randomized clinical trial. *Am J Emerg Med.* 2017;35:1810-4.
26. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med.* 2018;378:797-808.
27. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med.* 2018;378:809-18.
28. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic Shock: 2016. *Crit Care Med.* 2017;45:486-552.
29. Tavaré A, O'Flynn N. Recognition, diagnosis, and early management of sepsis: NICE guideline. *Br J Gen Pract.* 2017;67:185-6.
30. Annane D, Pastores SM, Rochweg B, Arlt W, Balk RA, Beishuizen A, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med.* 2017;43:1751-63.
31. Lamontagne F, Rochweg B, Lytvyn L, Guyatt GH, Møller MH, Annane D, et al. Corticosteroid therapy for sepsis: A clinical practice guideline. *BMJ.* 2018;362:k3284.
32. Nishida O, Ogura H, Egi M, Fujishima S, Hayashi Y, Iba T, et al. The Japanese clinical practice guidelines for management of sepsis and septic shock 2016 (J-SSCG 2016). *Acute Med Surg.* 2018;6:7.
33. Gordon AC, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the vanish randomized clinical trial. *JAMA.* 2016;316:509-18.
34. Annane D. Why my steroid trials in septic shock were "positive"? *Crit Care Med.* 2019;47:1789-93.
35. Heming N, Sivanandamoorthy S, Meng P, Bounab R, Annane D. Immune effects of corticosteroids in sepsis. *Front Immunol.* 2018;9:1736.
36. Hamitouche N, Comets E, Ribot M, Alvarez JC, Bellissant E, Laviolle B. Population pharmacokinetic-pharmacodynamic model of oral fludrocortisone and intravenous hydrocortisone in healthy volunteers. *AAPS J.* 2017;19:727-35.
37. Arriza JL, Weinberger C, Cerelli G, Glaser TM, Handelin BL, Housman DE, et al. Cloning of human mineralocorticoid receptor complementary DNA: structural and functional kinship with the glucocorticoid receptor. *Science.* 1987;237:268-75.
38. Lombes M, Kenouch S, Souque A, Farman NI, Rafestin-Oblin ME. The mineralocorticoid receptor discriminates aldosterone from glucocorticoids independently of the 11 beta-hydroxysteroid dehydrogenase. *Endocrinology.* 1994;135:834-40.
39. Sellick J, Aldridge S, Thomas M, Cheetham T. Growth of patients with congenital adrenal hyperplasia due to 21-hydroxylase in infancy, glucocorticoid requirement and the role of mineralocorticoid therapy. *J Pediatr Endocrinol Metab.* 2018;31:1019-22.

40. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2016;101:364-89.
41. Moraes RB, Friedman G, Viana MV, Tonietto T, Saltz H, Czepielewski MA. Aldosterone secretion in patients with septic shock: a prospective study. *Arq Bras Endocrinol Metab.* 2013;57:636-41.
42. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
43. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol.* 2014;14:135.
44. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011;64:401-6.
45. COITSS Study Investigators, Annane D, Cariou A, Maxime V, Azoulay E, D'honneur G, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA.* 2010;303:341-8.
46. Laviolle B, Annane D, Fougerou C, Bellissant E. Gluco- and mineralocorticoid biological effects of a 7-day treatment with low doses of hydrocortisone and fludrocortisone in septic shock. *Intensive Care Med.* 2012;38:1306-14.
47. Arriza JL, Weinberger C, Cerelli G, Glaser TM, Handelin BL, Housman DE, et al. Cloning of human mineralocorticoid receptor complementary DNA: structural and functional kinship with the glucocorticoid receptor. *Science.* 1987;237:268-75.
48. Bookout AL, Jeong Y, Downes M, Yu RT, Evans RM, Mangelsdorf DJ. Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. *Cell.* 2006;126:789-99.
49. Ronzaud C, Loffing J, Bleich M, Gretz N, Gröne HJ, Schütz G, et al. Impairment of sodium balance in mice deficient in renal principal cell mineralocorticoid receptor. *J Am Soc Nephrol.* 2007;18:1679-87.
50. Fadel F, André-Grégoire G, Gravez B, Bauvois B, Bouchet S, Sierra-Ramos C, et al. Aldosterone and vascular mineralocorticoid receptors in murine endotoxic and human septic shock. *Crit Care Med.* 2017;45:e954-62.
51. Hicks CW, Sweeney DA, Danner RL, Eichacker PQ, Suffredini AF, Feng J, et al. Beneficial effects of stress-dose corticosteroid therapy in canines depend on the severity of staphylococcal pneumonia. *Intensive Care Med.* 2012;38:2063-71.
52. Hicks CW, Sweeney DA, Danner RL, Eichacker PQ, Suffredini AF, Feng J, et al. Efficacy of selective mineralocorticoid and glucocorticoid agonists in canine septic shock. *Crit Care Med.* 2012;40:199-207.
53. du Cheyron D, Lesage A, Daubin C, Ramakers M, Charbonneau P. Hyperreninemic hypoaldosteronism: a possible etiological factor of septic shock induced acute renal failure. *Intensive Care Med.* 2003;29:1703-9.
54. Usher MG, Duan SZ, Ivaschenko CY, Frieler RA, Berger S, Schütz G, et al. Myeloid mineralocorticoid receptor controls macrophage polarization and cardiovascular hypertrophy and remodeling in mice.

J Clin Invest. 2010;120:3350-64.

55. Keidar S, Kaplan M, Pavlotzky E, Coleman R, Hayek T, Hamoud S, et al. Aldosterone administration to mice stimulates macrophage NADPH oxidase and increases atherosclerosis development: a possible role for angiotensin-converting enzyme and the receptors for angiotensin II and aldosterone. *Circulation*. 2004;109:2213-20.
56. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36:296-327.
57. Coursin DB, Wood KE. Corticosteroid supplementation for adrenal insufficiency. *JAMA*. 2002;287:236-40.
58. Huh JW, Choi HS, Lim CM, Koh Y, Oh YM, Shim TS, et al. Low-dose hydrocortisone treatment for patients with septic shock: a pilot study comparing 3 days with 7 days. *Respirology*. 2011;16:1088-95.

Tables

Table 1. Result According to Control Group

Outcome		Risk Ratio (95% confidential interval)		
		Overall	vs Corticosteroid-free	vs Hydrocortisone-only
Mortality	28-day mortality	0.88 (0.78–0.99)	0.88 (0.78–0.99)	N/A
	In-hospital mortality	0.89 (0.81–0.97)	0.88 (0.80–0.98)	0.91 (0.75–1.11)
	Long-term mortality	0.90 (0.83–0.98)	0.89 (0.81–0.97)	0.94 (0.78–1.13)
Shock reversal	Vasopressor withdrawal at day 28	1.06 (1.01–1.12)	1.06 (1.01–1.12)	N/A
	Vasopressor-free days up to day 28 (<i>days</i>)	2.0 (0.8–3.2) ^a	2.0 (0.8–3.2) ^a	N/A
Adverse events	Superinfection	1.14 (0.85–1.51)	1.08 (0.86–1.35)	1.54 (1.05–2.26)
	GI bleeding	0.96 (0.66–1.39)	0.96 (0.66–1.39)	N/A
	Hyperglycemia	1.07 (1.03–1.12)	1.07 (1.03–1.12)	N/A
	Psychiatric disorders	0.33 (0.01–8.06)	0.33 (0.01–8.06)	N/A

Bold indicates that there is a significant difference. GI = gastrointestinal, ^a Vasopressor-free days were presented as mean difference.

Table 2. Summary of Finding Table

Outcomes	No. of Studies	No. of Patients		Effect Estimates		Certainty in Effect Estimates	Certainty Assessment
		HC+FC	Control	Relative Effect	Absolute Effect		
				(95% CI)	(95% CI)		
28-day mortality	2	289/764 (37.8%)	335/776 (43.2%)	RR 0.88 (0.78 to 0.99)	52 fewer per 1,000 (4 fewer to 95 fewer)	⊕⊕⊕⊕ High	
Long-term mortality (90 day to 1 year)	3	478/1009 (47.4%)	548/1040 (52.7%)	RR 0.90 (0.83 to 0.98)	53 fewer per 1,000 (11 fewer to 90 fewer)	⊕⊕⊕⊕ High	
Shock Reversal (at day 28)	1	603/761 (79.2%)	569/775 (73.4%)	RR 1.06 (1.01 to 1.12)	44 more per 1,000 (7 more to 88 more)	⊕⊕⊕ Moderate	Imprecision
Superinfection	3	266/1009 (26.4%)	242/1039 (23.3%)	RR 1.14 (0.85 to 1.51)	33 more per 1,000 (35 fewer to 119 more)	⊕⊕ Low	Borderline inconsistency and imprecision
GI bleeding	2	50/764 (6.5%)	53/775 (6.8%)	RR 0.96 (0.66 to 1.39)	3 fewer per 1,000 (23 fewer to 27 more)	⊕⊕ Low	Serious imprecision
Hyperglycemia	3	547/614 (89.1%)	520/626 (83.1%)	RR 1.07 (1.03 to 1.12)	58 more per 1,000 (25 more to 100 more)	⊕⊕⊕⊕ High	
Psychiatric disorders	3	0/150 (0%)	1/149 (0.7%)	RR 0.33 (0.01 to 0.65)	4 fewer per 1,000 (6 fewer to 18 more)	⊕⊕ Low	Serious imprecision

HC = hydrocortisone, FC = fludrocortisone, GI = gastrointestinal, CI = confidential interval, RR = risk ratio, Certainty in effect estimates was assessed with five domains (study limitations, inconsistency, indirectness, imprecision, and publication bias).

Figures

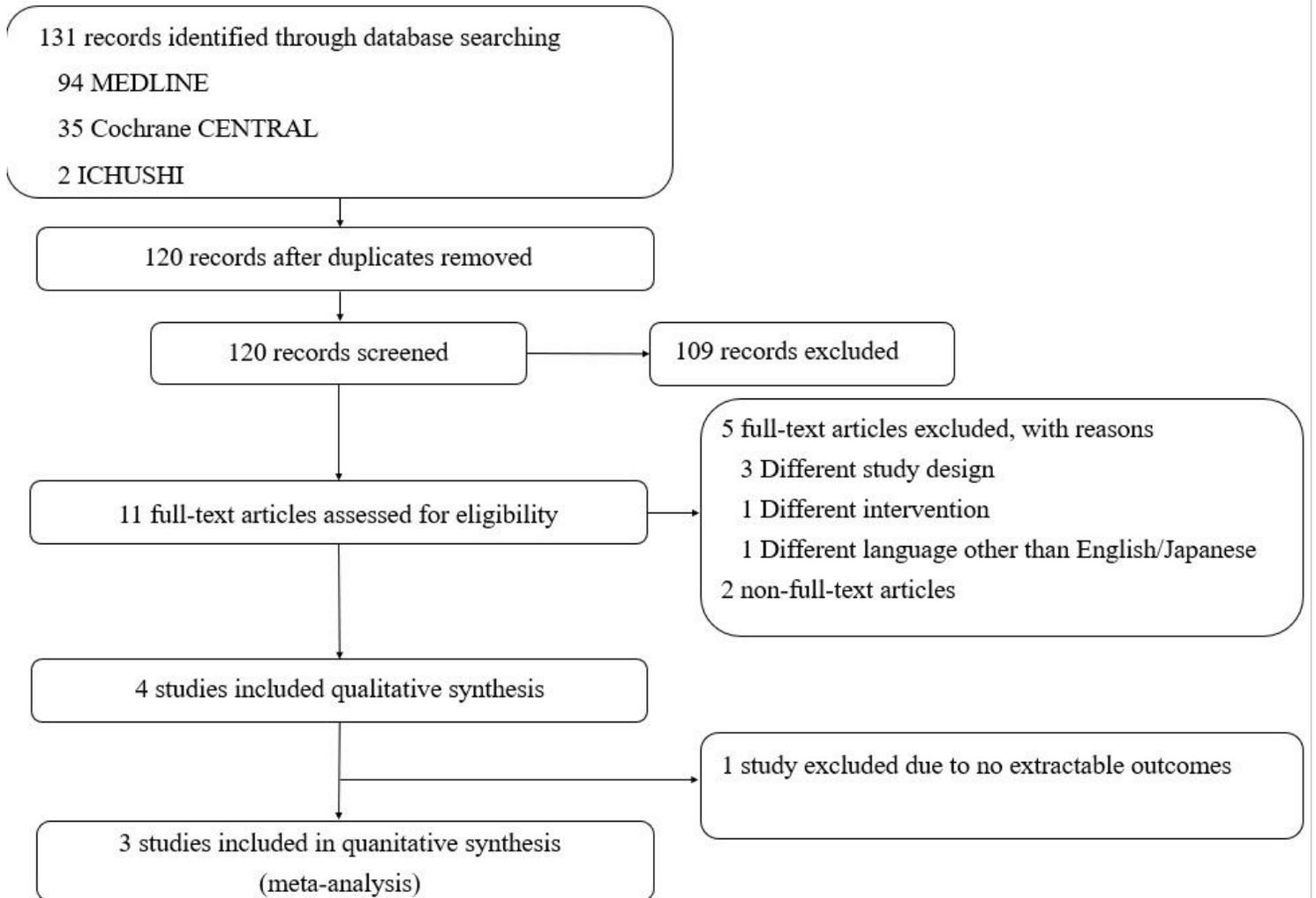
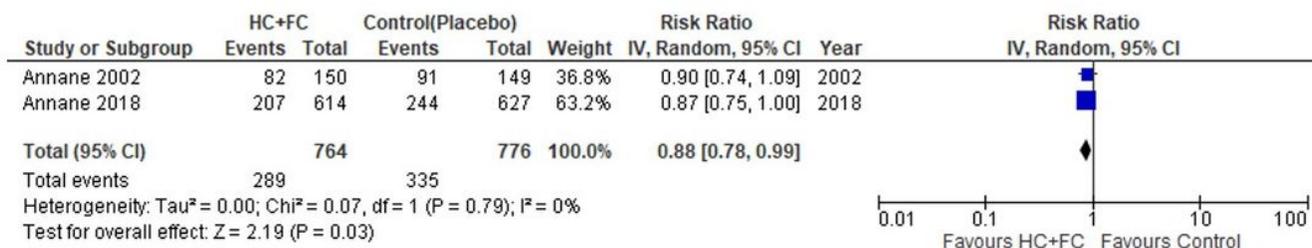


Figure 1

Study selection flow diagram Among four studies eligible for data synthesis, a total of 2050 patients from three studies were included for quantitative synthesis

A



B

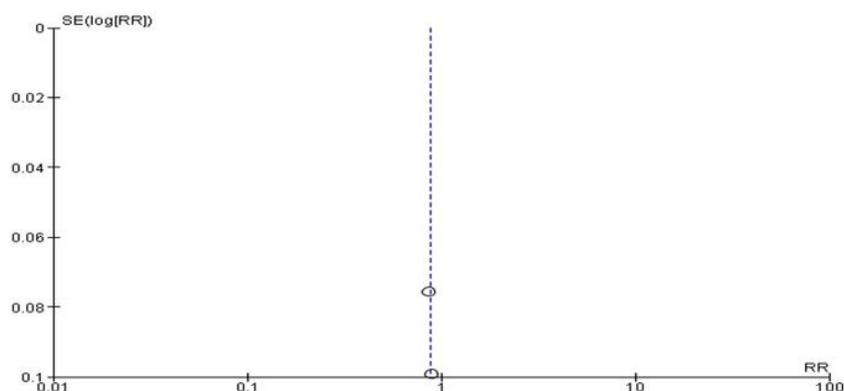
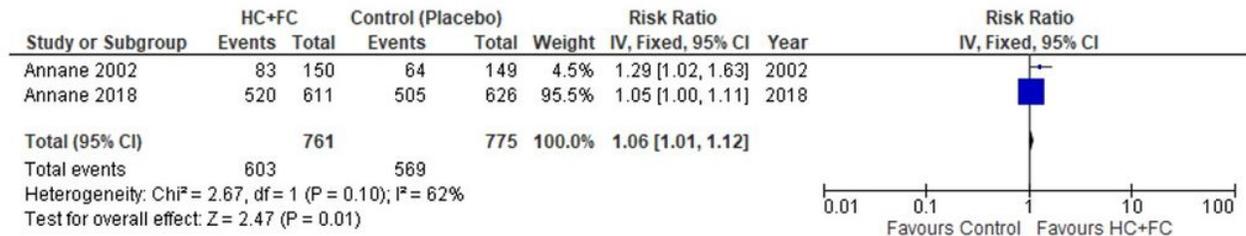


Figure 2

A, Forest plots of 28-day mortality in the dual corticosteroid treatment and corticosteroid-free groups. B, Funnel plot of publication bias analysis HC, hydrocortisone; FC, fludrocortisone; df, degrees of freedom; IV, inverse variance; RR, risk ratio

A Shock reversal at day 28



B Vasopressor-free days up to day 28

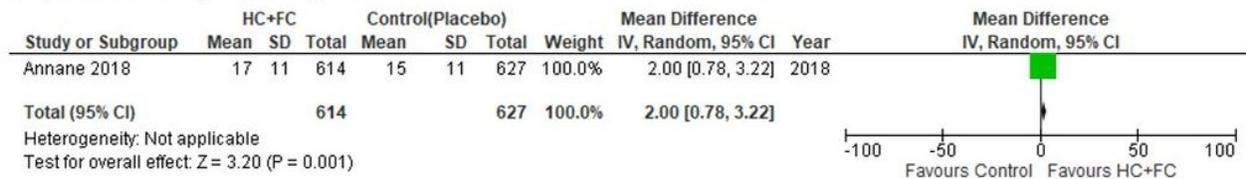


Figure 3

A, Forest plot of shock reversal on day 28. B, Forest plot of vasopressor-free days up to day 28 HC, hydrocortisone; FC, fludrocortisone; IV, inverse variance

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